Medical and Pediatric Oncology 27:415–421 (1996)

Screening for Wilms' Tumor in Children With High-Risk Congenital Syndromes: Considerations for an Intervention Trial

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Screening for cancer in children is uncommon. However, in children with congenital syndromes associated with Wilms' tumor, conditions exist that potentially make screening effective. This select population of children 1) are relatively easily identified; 2) have a high incidence of Wilms' tumor; 3) if identified before development of Wilms' tumor, may have a decrement in morbidity/mortality; and 4) are amenable to a simple and acceptable screening technology, renal sonography exams.

Many clinicians have recommended screening for cancer in children with congenital syndromes associated with Wilms' tumor. However, neither costs nor effectiveness of such recommendations have been evaluated systematically. The strongest evidence for or against Wilms' tumor screening in this select population would be provided by a randomized screening trial. Prior to undertaking such a trial, the key parameters that dominate the cost and effectiveness of screening should be identified. Simulation models, such as cost-effectiveness analysis, offer a starting point for deciding whether cancer screening is appropriate, and if so, under what set of conditions.

We review basic conditions required for a successful screening trial in children with syndromes that are at increased risk of Wilms' tumor. We also discuss the use of cost-effectiveness analysis as a preliminary step in determining the feasibility of an intervention trial.

Key words: cancer screening, Wilms' tumor, intervention trial

INTRODUCTION

Miller et al. [1] were the first to describe the association between congenital syndromes and Wilms' tumor. Their seminal article identified idiopathic hemihypertrophy and aniridia as the first two congenital syndromes associated with Wilms' tumor. Subsequently, children with Beckwith-Wiedemann syndrome (BWS) [2], Perlmann syndrome [3], and possibly Sotos syndrome [4] have been observed to have an increased risk of Wilms' tumor. The awareness of the increased risk of Wilms' tumor in patients with selected congenital syndromes coupled with the increased availability of sonography has raised the issue of whether screening for Wilms' tumor in this population is appropriate. Current practice varies from no screening [5] to periodic screening every 3–12 months [6,7]. What group of patients to screen, how frequent to screen, and when to stop screening have not been established. Thus far, recommendations for screening have been based on expert opinion [8], limited case reports [6,7], and two case series of 41 [9] and 159 [10] high-risk patients for Wilms' tumor. Although these studies are valid starting points, more rigorous quantitative techniques are required to address the benefit of screening for Wilms' tumor in this select population.

Evidence for or against cancer screening has been based traditionally on three different analytical methods: randomized clinical trials, case control studies, and case series. The strongest evidence for cancer screening is obtained from randomized cancer screening trials. However, randomized screening trials are typically expensive, elaborate, and require several years duration before a result is known. The next method of choice is a case-control screening study. Such studies are always retrospective, are open to self-selection bias [11], and have reduced capability to adjust for risk factor differences between screened and nonscreened individuals [12]. Nevertheless, case-control studies present a reasonable alternative when a screening trial cannot be implemented or the results will not be available for many years. Case series provide the third and weakest form of evidence for cancer screening. Such series usually reflect the experience of a single institution and have several limitations including observer bias, secular trends, and no contemporary comparison group. Nonetheless, such observations may provide an important impetus to more formal investigation.

Recently, simulation models such as those used in decision analysis or cost-effectiveness analysis have been

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Received August 27, 1995; accepted February 6, 1996.

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used as an initial analytical technique to assist in designing cancer screening trials. Such models use data from heterogeneous sources identifying the most dominant parameters for a proposed cancer screening trial [13].

In this paper, we will review the principles of cancer screening that have specific application for children at risk for Wilms' tumor. In addition, we will discuss the most important variables required for a cost-effectiveness analysis to determine the feasibility of a Wilms' tumor screening trial in this select population.

CANCER SCREENING PROGRAMS IN CHILDREN

The principles of cancer screening for Wilms' tumor in children are similar to the principles for screening in any chronic disease. These principles have been discussed in depth elsewhere [14,15]. Five of these principles have particular relevance to screening in children with high-risk syndromes associated with Wilms' and will be discussed in detail. First, early treatment or detection should result in a decreased mortality and/or morbidity; second, age-specific incidence should be high enough to warrant screening; third, the population at risk should be easily identified; fourth, the natural history of the cancer should be known; and fifth, the screening test must be easy to administer, acceptable, and accessible to the target population.

Clinical Benefit of Early Detection of Cancer

The major premise in cancer screening is that early detection will result in a decrease in mortality and/or morbidity. Although the potential for this decline exists, there are little data on children to show that early detection of cancer will decrease mortality or morbidity. In Wilms' tumor, survival is primarily dependent on stage and histology [16]. Only the stage of Wilms' tumor at the time of diagnosis can be altered with cancer screening. Nevertheless, survival is substantially different between stages I thru IV [16], resulting in a potential benefit of early detection of Wilms' tumor. The 5-year survival rates for stage I, II, III, and IV favorable histology Wilms' tumor are 97, 94, 88, and 82 respectively [17].

Given the high survival rate for Wilms' tumor, future screening for children with high-risk syndromes will need to include morbidity as well as mortality as outcome measures. The primary measure of morbidity in this population can be assessed as a downward stage shift from advanced disease (stage III or IV) to more localized disease (stage I or II). Such a downward stage shift will result in decreased acute and long-term sequelae, since patients with stage I and II Wilms' tumor do not receive Adriamycin and radiation therapy; patients with stage III and IV disease do receive these more toxic therapies.

To date no study has proved the efficacy of screening for Wilms' tumor in a high-risk population. In a limited study by a European group, investigators demonstrated that children with congenital syndromes predisposing to Wilms' tumor who were screened had the same mortality rate as children who were not screened [9]. The major limitation of the study was the small sample size of 41 patients. Consequently, the study may not have had enough patients to detect a statistical difference if it existed between the screened and nonscreened groups. The study would have required a total of 200 patients with high risk congenital syndromes who developed Wilms' tumor to show a 10% difference in survival (based on an alpha level of 0.05 and beta level of 0.1) [9]. If one assumes a 10% frequency of cancer in this subgroup, approximately 2,000 high risk children would have to be followed from infancy to early childhood to have enough patients for such a trial. Given the rarity of these syndromes, the prospects of completing such a trial in a reasonable period of time are limited. Even if Craft et al. [9] had used a downward stage shift distribution as the primary outcome measure, the study still would not have had adequate power to determine a statistical difference in stage shift distribution between screened and unscreened patients. The study would have required 40 screened patients with high-risk syndromes and Wilms' tumor instead of the 13 patients studied (based on an alpha level of 0.05, beta 0.2, and a decrease in the proportion of stage III and IV patients from 0.27, the proportion usually seen in unscreened children, to 0.01).

Age-Specific Cancer Incidence Is High Enough to Warrant Cancer Screening

The incidence of cancer in children is too low to justify population-based screening for the most common pediatric cancers. A preliminary report has suggested that even for neuroblastoma, the most frequent childhood solid tumor (3 cases per 100,000 infants less than 1 year old) [18], population-based screening is not likely to be cost-effective [19]. Only when the age-specific incidence of cancer approaches the range seen in adult cancers, such as breast cancer for women greater than 50 years of age (304 per 100,000 women older than 50 years of age per year) [20] or colon cancer for adults greater than 50 years of age (183 per 100,000 adults older than 50 years of age per year) [20], can there be an anticipated benefit of cancer screening in children. Thus, children with cancer predisposition syndromes comprise the only subgroup with a sufficiently high enough cancer incidence to potentially benefit from an intervention program.

To assess the feasibility of a Wilms' tumor screening trial and to determine when to start and stop screening, the age-specific incidence of Wilms' tumor must be determined. In order to determine the age-specific incidence, we need to know the age at which patients with selected congenital syndromes develop Wilms' tumor, as well as the total number of children with the specific clinical

phenotype. Typically, the numerator, the number of patients with the congenital syndrome who developed cancer, can be easily obtained from chart review or published data. However, the denominator, the total number of patients with the congenital syndrome at risk for developing Wilms' tumor, is more difficult to identify. Commonly, calculation of the denominator requires a prospective study or a registry of patients who have a cancer predisposition syndrome. Such registries have been difficult to start. Nevertheless, national registries for cancer predisposition syndromes such as Fanconi anemia [21], Bloom syndrome [22], and ataxia telangiectasia [23] have provided important data regarding the age-specific risk of cancer and the natural history of these rare syndromes. Currently, the Beckwith Wiedemann Syndrome Registry is the only national registry for patients with a syndrome associated with Wilms' tumor. This registry was initiated at the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. Preliminary data from this registry indicate that the peak incidence of Wilms' tumor in children with BWS is 2,850 cases per 100,000 patients per year and occurs between the first and second birthday (personal communication).

Screened Population Easily Identified

A major premise of cancer screening is that the target population can be identified easily. In adult cancer screening programs, at-risk groups have traditionally been demarcated by age. For example, mammography is recommended for women older than 50 years of age and fecal occult blood testing is suggested for adults older than 50 years of age. Identification of these groups has been straightforward. However, accurate identification of children with congenital syndromes at risk of Wilms' tumor is not easily accomplished.

Among the congenital syndromes associated with Wilms' tumor, aniridia with or without genitourinary abnormalities is the only clinical phenotype that is easily recognized. The overgrowth syndromes, including Beckwith Wiedemann, Perlman, Sotos, and idiopathic hemihypertrophy, are defined by both subjective and objective components. Thus, the diagnosis of an overgrowth syndrome in a child is often dependent upon clinical impression rather than a formal definition. Despite misclassification of diagnosis, partial characteristics of an overgrowth syndrome are sufficient to identify a group at increased risk for Wilms' tumor [2]. Because of the subjective nature of diagnosis of overgrowth syndromes, a minimum set of objective criteria should be established prior to the onset of a cancer screening trial.

Natural History of the Cancer Is Known

The natural history of cancer refers to the clinically relevant phases from the beginning of the biological life of cancer to the death of the patient. It is an important but elusive parameter that needs to be defined when trying to establish a cancer screening program. The natural history of cancer cannot be measured directly; however, when cancer screening is done, discrete time periods can be identified and combined, providing a reasonable estimate of the natural history. The preclinical and the clinical phase describe the two discrete periods that make up the entire natural history of a cancer. The boundary between the preclinical and clinical phase varies from patient to patient, based on numerous factors, including access to health care and biological character of the cancer. The preclinical period starts at the biological life of the tumor and ends at the beginning of the clinical phase. It can be divided further into the nondetectable and the detectable preclinical phases. The threshold between these two phases refers to the earliest period of time that the cancer can be detected when screening is done (Fig. 1). Only the detectable preclinical phase of cancer can be estimated from a cancer screening program. This period is dependent upon the technology used to screen as well as the inherent biologic nature of the cancer. Within the detectable preclinical phase, the lead time resulting from cancer screening can be determined. The lead time refers to the interval that the diagnosis is advanced by a specific screening program [24]. The empirical determination of the lead time requires, among other things, information on prevalence and incidence of the cancer in the screened population and assumptions about the rate of growth of the tumor. For a more detailed determination of how lead time is determined, the reader is referred to Walter and Day [25]. Currently insufficient data exist to determine lead time in children screened with sonography exams for Wilms' tumor.

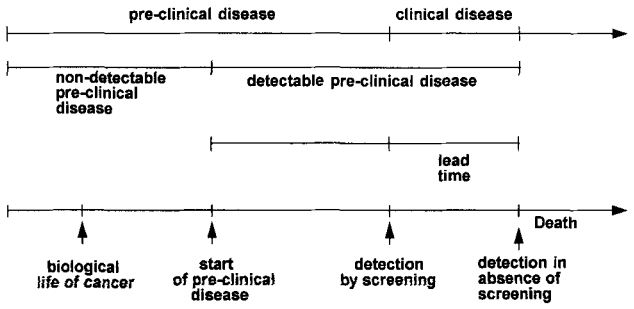

Fig. 1. Relationship between duration of preclinical disease, detectable preclinical disease, and lead time.

Once the decision has been made to screen for cancer, the screening interval must be determined. In cancer screening programs for adults, screening guidelines may vary by as much as 24 months for the same tumor. For example, recommended screening intervals for breast cancer vary from 1 to 3 years [26]. Given the rapid growth rate of many childhood cancers when compared to adult cancers, such wide variation in the screening interval for

childhood cancer is not practical. As an illustration, the upper and lower estimate of the doubling time for breast cancer is 120 to 365 days [27]; whereas, for Wilms' tumor the upper and lower estimates of doubling times range from 17 to 40 days [28].

The relationship between lead time and screening interval was established by Dwyer and colleagues [29]. They demonstrated that the screening interval should be based on the age-specific hazard of developing cancer and should not be longer than the lead time for the cancer. In the case of Wilms' tumor, both the age-specific hazard of Wilms' tumor in high-risk syndromes and the lead time are unknown. Despite the paucity of data regarding the natural history of Wilms' tumor, the upper limit of a screening interval can be estimated based on case reports in high-risk patients receiving surveillance renal sonography. Case reports have shown that Wilms' tumor has developed in 3 and 6-month screening intervals of surveillance renal sonography [5–7]. Based on these limited observations and the fact that the screening interval should not be longer than the detectable preclinical phase, the maximum screening interval for Wilms' tumor should be a maximum of 4 months. As more children with high-risk syndromes are screened with renal sonography, better estimates of the natural history of Wilms' tumor should be available.

The Screening Method Should Be Easy to Apply, Acceptable, and Accessible

Screening for cancer in children represents a unique challenge since anxiety, discomfort, and time spent for the procedure pertain not only to the child but also to parents. Technology requiring sedation or long periods of evaluation are not generally acceptable as routine surveillance procedures for Wilms' tumor. Examples of such methods include magnetic resonance imaging or computed tomography scan, both of which require oral sedation or general anesthesia in young children. Furthermore, parents are not likely to subject their children to these risks three to four times a year for several years when the benefit is not confirmed.

As an alternative renal sonography, the current modality used to screen some patients with Wilms' tumor, is a simple, safe, noninvasive procedure and is easily done in infants and children. Furthermore, most if not all hospitals where children are treated have access to an ultrasound machine and a radiologist to review the ultrasound images. If Wilms' tumor screening becomes standard clinical practice for children with high-risk syndromes, renal sonography will most likely be the applied technology.

COST-EFFECTIVENESS MODEL FOR DEVELOPMENT OF A CANCER SCREENING TRIAL

Cost-effectiveness models have frequently been used to assess the relative merits of different cancer screening modalities. Such analyses have provided the basis for determining the optimal age and screening interval for mammography to detect breast cancer [26]. An additional use of cost-effectiveness analysis is as a preliminary step to identify key outcome measures before starting a cancer screening trial. It is on this latter use of cost-effectiveness analysis that our discussion will focus. We will first introduce some of the terms and concepts associated with cost-effectiveness analysis with attention to issues specific to children. This will be followed by a brief discussion of key data that must be collected prior to initiating a Wilms' tumor screening trial in high-risk children.

CONSIDERATIONS OF COST-EFFECTIVENESS IN CHILDHOOD SCREENING

Perspective

Economists recommend that the societal perspective should be applied to cost-effectiveness analysis in medicine [30]. This means that the cost and benefits should be conveyed in a way that society is considered the decision maker. However, in subsidiary analysis, other perspectives may also be considered, such as third-party insurers, parents, or employers. Depending on which perspective is selected in a cost-effectiveness analysis, the relevant costs as well as benefits must be explicitly defined. When applying cost-effectiveness analysis to cancer screening programs in children, the societal perspective should also be applied.

Costs

The entire cost of a cancer screening program can be elusive since costs are both direct and indirect. The direct costs include expenditures for the screening intervention, physician services, outpatient clinical care, hospitalizations, and other medial costs related to the diagnosis and care of the patient. In cost-effectiveness analysis, such costs have been exhaustively itemized only rarely. As an alternative approach to complete tabulation of all applicable medical costs, some cost-effectiveness analyses simply include the incremental cost of patients who received the screening intervention vs. those who do not. This approach reduces the task of identifying all the costs, which are typically not readily available, but runs the risk of missing costs that the analyst may not anticipate.

Unlike direct costs which are included in some form in all cost-effectiveness analysis, indirect costs are seldom included. Indirect costs refer to the time and economic opportunities lost by the patient, family, and others in order to accommodate the health care intervention. These costs are often difficult to quantify; nevertheless, they are important to assess. A simplified technique to determine indirect costs is a method referred to as willingness to pay. In this method the patient or caregiver is asked how much they would be willing to pay out of pocket to avoid a particular action. The underlying assumption is that the person will be able to accurately estimate an amount that

TABLE I. Age Interval, Frequency of Intervention, Incidence of Cancer, and Cost per Life Year Saved for Selected Cancers Where Screening is Recommended or Being Considered

Intervention	Age (years)	Frequency of intervention	Incidence (per 100,000)	Remaining life-time risk[a]	Cost per life year saved	Ref.
Fecal occult blood test of colon cancer	>50	Annual	183	6.3%[a]	$37,000	35
Cervical cancer screening	>65	Triennial	31	0.4%[a]	$41,000	37
Mammography screening	50–65	Biennial	304	11%[a]	$49,000	38
Colonoscopy screening for colon cancer	>50	Triennial	183	6.3%[a]	$57,000	35
VMA/HMV* urine test for neuroblastoma	0–0.5	Twice	3	0.01%	??	19
Ultrasonography for Wilms' tumor in children with BWS	0–8	Quarterly	2,850	10% (from age 0–10 years)	??	**[b]

[a]Life-time risk calculated by DEVCAN [20].
[b]Estimates based on data from BWS registry provided by the author.

is commensurate with their level of inconvenience from the activity.

Outcome Measures

In addition to quantifying costs, the effectiveness of the screening intervention must be assessed. In cancer screening programs effectiveness is commonly represented as the number of life years saved or quality adjusted life years saved. The number of life years saved is a primary means to express a decrease in mortality associated with the cancer intervention when the endpoint of the trial includes not only mortality but also quality of life and morbidity. However, such a measure underestimates the benefit of a cancer screening trial when considering the quality of life or a decrease in morbidity resulting from screening. Quality adjusted life years (QALY) allows for individual patient preferences to be assessed. However, before QALY is introduced in childhood trials, standardization of this outcome measure must be determined. Furthermore, when determining the QALY for a child, the impact of the quality of life on the family unit should be considered. To date no studies have addressed a complete assessment of QALY that includes both the perspective of the child and the family unit [31].

Discount Rate

Discounting is a technique used by economists to equate costs and benefits that occur in different time periods. Costs and benefits that take place in the future are worth less than those that occur in the current period. Discounting of costs and benefits is a separate and distinct adjustment from those made for the changing purchasing power of money for health care services. The latter is referred to as an adjustment for inflation. The rationale for applying a discount rate to cost-effectiveness analysis is based on two assumptions: 1) resources invested today will yield a return in future years; and 2) individuals have a time preference favoring the consumption of income or health benefits in the present over the future.

In the most cost-effectiveness analysis, both costs and health effects are uniformly discounted [32]. However, the level of discount costs and benefits is not accepted uniformly. The discount rate can range from 2% [33] through 10% [34], with the most cost-effectiveness analysis using a discount rate of 5%. For adult cancer screening programs, most of the costs and the benefits typically occur within the same decade. In these cases the value of the discount rate will have relatively little impact on the cost-effectiveness result. However, in the case of cancer screening for children, the costs and benefits can have widely divergent time spans. Costs will generally be concentrated at the beginning of the intervention, while benefits may continue for the life span of the patient. Thus, in a cost-effectiveness analysis involving children, using a discount rate of 10% may result in an unfavorable cost-effectiveness ratio. However, by using the same data, but changing the discount rate to 2%, the analysis may have a strongly favorable cost-effectiveness ratio.

Limitations of Cost-Effectiveness Analysis as a Preliminary Step for a Cancer Screening Trial

The use of cost-effectiveness analysis to identify key parameters of a cancer screening trial is a new application of this methodology. Such analysis relies heavily on a hypothetical cohort with key assumptions. Despite sensitivity analysis, this estimate may vary widely from actual trial data. Lastly, cost-effectiveness analysis cannot provide explicit criteria for what constitutes a fair allocation of health care resources. Despite the absence of good knowledge about specific parameters, cost-effectiveness analysis can often provide a systematic and comprehensive framework for identifying variables that are or are not important to policy.

SUMMARY OF IMPORTANT MEASURES REQUIRED FOR AN INTERVENTION TRIAL

Children with congenital syndromes associated with Wilms' tumor have the necessary conditions for a screening trial. These prerequisites include but are not limited to a group that can be identified; a potential for a decrease in mortality/morbidity if the cancer is identified early;

a sufficiently high enough incidence of cancer; and an acceptable technology for cancer screening. Children with high-risk syndromes have similarities with adults who are screened for breast cancer with mammography or colon cancer with fecal occult blood test (Table I). Based on adult cancer screening programs, the acceptable upper limit for Wilms' tumor screening in this select population will probably be between $50,000 and $75,000 per life year saved [35,36]. A case-control study showing the efficacy of screening children with a high risk syndrome followed by cost-effectiveness analysis based on a hypothetical cohort of children with high-risk syndromes are next steps to determine the most important parameters in a cancer screening trial in this population.

ACKNOWLEDGMENTS

We thank Alisa Goldstein, PhD, Dilys Parry, PhD, and Lea Harty, MPH, of the Genetic Epidemiology Branch of the National Cancer Institute for the helpful comments in preparation of the manuscript.

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ADDENDUM

The Beckwith Wiedemann syndrome (BWS) registry was started in 1992 to determine the natural history of cancer in this select population. We are actively recruiting children with BWS or idiopathic hemihypertrophy. We are particularly interested in enrolling those children who have had cancer.

Participation in the registry involves:

1. Signing an informed consent.
2. Signing an information release form to verify selected clinical findings.
3. Completion of a questionnaire (approximately 20 minutes).

Potential participants are enrolled in the study by their parents or legal guardians. All information is confidential and no information will be released to insurance companies or other researchers.

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COMMENTARY

In reviewing the basic conditions required for successful screening programs, DeBaun and colleagues propose that children with congenital syndromes associated with Wilms' tumor possess most of the necessary conditions for a screening trial. The incidence of Wilms' tumor in this population is sufficiently high, and there is an acceptable technology for cancer screening (although imaging studies have several limitations). If the "at-risk" group can be identified (although overgrowth syndromes are easily missed), early identification could result in a decreased morbidity (since stage 1 and 2 patients do not receive doxorubicin or radiotherapy). Despite their personal involvement in this novel field of research, the authors have not hesitated to present arguments both in favor as well as against screening for Wilms' tumor in children at increased risk. DeBaun et al. provide a much needed clear and concise critical analysis of this extremely important and controversial subject.